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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO
08/803,702	02/21/97	MAINO	V P-3639P1

EXAMINER

HM12/0327

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ART UNIT	PAPER NUMBER
GAMBEL, P	
1644	17

DATE MAILED: 03/27/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on _____

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 19-60 is/are pending in the application.
Of the above, claim(s) 34-38, 41-42, 44-45, 48, 58-60 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 19-33, 39, 40, 43, 46, 47, 49-57 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. The location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1644, Technology Center 1600.

2. Applicant's election of Group I and the species anti-γIFN, anti-CD4, anti-CD28, viral antigen and CMV antigen in Paper No. 15 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without.

Claims 19-33, 39, 40, 43, 46 ,47 and 49-55 are under consideration.

Accordingly, claims 34-38, 41, 42, 44, 45, 48 and 56-60 are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

Claims 1-18 have been canceled previously.

3. The Information Disclosure Statement, filed 3/12/99 (Paper No. 11), is acknowledged.
Applicant is invited to provide the date for Maino et al. Fast Immune Assay System, Becton Dickinson Immunocytometry Systems reference.

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

Photographs are not acceptable until petition is granted as set forth in 37 CFR 1.84(b). Under 37 CFR 1.84(b), the applicant must file a petition with fee requesting acceptance of the color photographs. The petition is decided in the Office of the Group Director.

The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

5. In view of the papers filed 3/12/99 (Paper No. 12), it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(c). The inventorship of this application has been changed by adding Louis Picker to the inventive entity.
The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The amendment filed 3/12/99 (Paper No. 10), is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: replacing "CD40" with "CD40L" on page 5 of the specification.

Applicant's amendment, filed 3/12/99 (Paper No. 10), asserts that CD40 does not appear on the surface of T lymphocytes; while the CD40L is the costimulatory molecule on T cells.

Although applicant appears to assert that both the error and the correction must be obvious in the specification with respect to CD40/CD40L; this is not necessarily the case.

For example, Lipsky et al. (NY Acad Sci 815: 372 -383, 1997; Conference held on 5/21-25/96) discloses T cell expression of CD40, including activated T cells (see pages 380-381).

Applicant is required to cancel the new matter in the reply to this Office action.

8. Claims 19-33, 39, 40, 43, 46 ,47 and 49-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "measuring expression of the one or more intracellular cytokines γ-IFN, IL-2, IL-4, IL-5, IL-10 and TNF-α; measuring the early activation antigen CD69; or providing the costimulus via CD28, CD40, CD86 or CD118, does not reasonably provide enablement for any intracellular cytokine, early activation antigen or costimulus in measuring .

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims

Applicant has not enabled measuring expression of one or more intracellular cytokines other than γ-IFN, IL-2, IL-4, IL-5, IL-10 and TNF-α; measuring an early activation antigen other than CD69; or providing a costimulus other than via CD28, CD40, CD86 or CD118. The specification does not appear to specifically define the metes and bounds of "intracellular cytokines", "costimulus" or "early activation antigen" a costimulatory signal in the T cell". As such, these terms cannot be considered to be limited to the specific use of the specificities indicated above to determine antigen specific activation of T cells, as claimed or disclosed in the specification. It is not sufficient to define a specificity by its principal biological activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed cytokines, activation antigens or costimuli in manner reasonably correlated with the scope of the claims broadly including any number of costimulatory signals or specificities. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Applicant's arguments, filed 3/12/99 (Paper No. 10), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments in conjunction with the commercial availability of cytokine-specific antibodies from Becton Dickinson in 1998 is acknowledged.

However, it is not clear how the specification as filed provides direction and guidance to detecting cytokines in the instant methods other than that indicated in the specification as filed and above.

Similarly, applicant's argues that the skilled artisan would recognize early activation antigens would refer to those cell surface proteins that reliably appear on the surface of T lymphocytes early in stereotypical activation process.

However, it is not clear how the specification as filed provides direction and guidance to detecting early activation antigens other than CD69 indicated in the specification as filed and above.

Applicant's provision of evidence that costimulatory activation via VLA-4 and CD5 is acknowledged.

However, it is not clear how the specification as filed provides direction and guidance to providing costimulatory activation other than targeting CD28, CD40, CD86 or CD118 indicated in the specification as filed and above.

Applicant's arguments are not found persuasive.

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 C.F.R. § 102(f) or (g) prior art under 35 C.F.R. § 103.

11. Upon reconsideration of applicant's amended claims and arguments, filed ; the previous rejection under 35 U.S.C. § 102(b) as being anticipated by Picker et al. (Blood, 1995) has been withdrawn as it applies to the instant claims reciting nominal antigen.

12. Claims 19-33, 39, 40, 43, 46 ,47 and 49-55 are rejected under 35 U.S.C. § 103 as being unpatentable over Picker et al. (Blood, 1995) in view of art known procedures to use cationic chelating agents in flow cytometry, as evidenced by Seon et al. (U.S. Patent No. 5,407,805), to lyse red blood cells, as evidenced by Schwartz (U.S. patent No. 5,093,234) and in view of art known motivation to detect antigen specific activation to a wide variety of antigens at the time the invention was made and further in view of Lolli et al. (FEMS Immun. Med. Microbiol. 7: 55-62, 1993; 1449) AND/OR Lolli et al. (AIDS Res. Human Retroviruses 10: 115-120, 1994; 1449).

Picker et al. teach the instant claims are drawn to a method of determining the antigen specific activation of T cells including the claimed specificities and limitations. .

Picker et al. differs from the instant methods by not teaching all of the claimed costimuli, however by teaching CD28, it would have led the ordinary artisan to apply other known T cell costimuli at the time the invention was made

Picker et al. differs from the instant methods by not teaching the art known lysis of RBCs and washing to remove debris from cell preparations for culture and FACS analysis, as evidenced by Schwartz and well-practiced at the time the invention was made, particularly with animal cells.

Picker et al. differs from the instant methods by not teaching the use of EDTA in washing cells, however this has long been used to prevent cell clumping and to reduce background in fluorescence, as known in the art at the time the invention was made or as evidenced by Seon et al. (U.S. Patent No. 5,407,805).

Picker et al. differs from the instant methods by teaching the term immunosuppressive or immunoaugmenting agent per se, however this reference does teach activation via PMA, ionomycin and superantigens. Also this reference discusses the broad importance of this assay in measuring and monitoring immune status. Therefore, it would have been obvious to the ordinary artisan to apply a number of immunomodulating agents, including both stimulatory and suppressive to the referenced system in analyzing immune functions of various cell populations at the time the invention was made.

Picker et al. differs from the instant methods by using polyclonal activators or superantigen stimulation. Picker et al. differs from the instant methods by not teaching all of the antigens encompassed by the claims per se, however this reference refers to the manifestation of immunity either protective or pathologic depends on the functional activity of memory/effector T cell subsets. Also, the specification acknowledges that there were a number of assays known in the art to detect antigen specific activation of T cells and that the difference of the instant application is drawn to the multi parametric flow cytometry analysis. Therefore the ordinary artisan was well motivated to apply various analyses to detect antigen specific activation of T cells.

Both Lolli et al. references teach and provide an expectation of success in detecting antigen-specific responses, including T cells response to CMV antigen, including measuring the production of cytokines (e.g. γIFN) from single T cells (see entire documents, including Abstracts, Results and Discussion).

One of ordinary skill in the art at the time the invention was made would have been motivated to select multi parametric flow cytometry analysis to determine antigen specific activation of T cells to a wide variety of antigens, including CMV antigens, to provide an useful tool to analyze and characterize T cell immunity with a high degree of specificity and sensitivity. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Applicant's amendment, filed 3/12/99 (Paper No. 10), have been fully considered as they apply to newly added claims but are not found convincing for the reasons herein.

Applicant argues that the prior art, including Picker, neither disclose nor suggest the possibility of using antigen specific stimuli to effect antigen-specific stimulation for the purposes of subsequent flow cytometric analysis. Applicant asserts that the use of polyclonal mitogens and superantigens to stimulate relatively large number of T cells, while fewer T lymphocytes would be activate by an antigen-specific stimulus. In turn, applicant asserts that the prior art results would not have suggested that antigen-specific stimulation would not produce sufficient numbers of activated T cells to permit the detection of individual cytokine production. Therefore, applicant asserts the instant methods were unpredicted and surprising in view of the prior art. In addition, applicant's argues that the various conditions, encompassing Brefeldin, costimulatory molecules and EDTA in the instant methods were similarly unexpected and unpredicted in view of the prior art.

In contrast to applicant's arguments, Picker et al. teach the use determining and understanding the entire physiologic range of T cell functional heterogeneity, encompassing assessing cytokine synthesis capabilities (e.g. γIFN, IL-2 and IL-4) of memory/effector T cells on a single cell basis by using intracytoplasmic staining and flow cytometry to assess T cell cytokine production (see entire document, including the Discussion as well as pages 1408-1409, overlapping paragraph). Here, Picker states that the results confirm an extensive heterogeneity in the ability of memory/effector T cells to produce these cytokines in response to both accessory cell-dependent and accessory cell-independent stimuli and show reproducible patterns of cytokine secretion by these cells. The direct visualization of T cell effector responses afforded by this unparalleled ability to determine the functional potential of phenotypically distinct T cells subset providing the opportunity to evaluate the participation of T cell subsets in human immune responses.

It is noted that Picker et al. As well as the Lolli references teach measuring cytokine production (e.g. γIFN) from single T cells.

While Picker teaches the use of PMA/Ionomycin and superantigen stimulation; Picker et al. teaches enhanced sensitivity and reproducibility of the flow cytometric cytokine production assays for both accessory cell-dependent and -independent T cell agonists (see Material and Methods, Flow Cytometric Cytokine Production Assays). Picker et al. Also teaches the use of leukocytes form DTH sites, including those exposed to common skin-test antigens such as mumps (see Materials and Methods, Cell Preparation). It is noted that page 17/Figure 2 of the instant specification disclose that T cell response to mumps antigens as well as CMV antigens can be measured.

It is noted that Picker et al. teaches that anti-CD3 plus anti-CD28 yields analogous cytokine-producing subsets (see page 1416, column 2, paragraph 1).

Picker et al. discloses that the specific cytokine phenotype of adoptively transferred murine T cell clones are retained for prolonged periods in vivo (see pages 1417--1418, overlapping paragraph), indicating that antigen-specific responses were amenable to the prior art methods.

Picker et al. also discusses the value of flow cytometric quantitation of the cytokine-defined memory/effector T cell subsets would prove invaluable in both the diagnosis and monitoring pathologic immunodeficiency and therapeutic immunosuppression and the human subsets observed may represent intermediate forms that will terminally differentiate upon further encounter with antigen or relevant microenvironmental antigen (page 1418, column 1, paragraphs 1-2).

While applicant asserts that the prior art method would not be expected to work on antigen-specific responses due to assay conditions as well as frequency of antigen-specific T cells. However, the prior art does not provide for such limitations of the prior art methodology to detect antigen-specific responses either by the use of antigen, which was shown to stimulate T cell at single cell levels, as evidenced by Lolli et al.. Also, it is clear that Picker et al. Teaches the value of the multi parametric flow cytometry assays to detect memory/effector cells, which would provide an expectation of success as well as motivation in detecting antigen-specific T cells at the single cell levels.

Applicant's arguments are not found persuasive.

Applicant is invited to consider to provide the conditions set forth on page 17, paragraph 1 of the instant specification into the independent claim and to provide objective evidence that such conditions provide for unexpected sensitivity.

12. The previous provisional double patenting rejections have been under 35 U.S.C. 101 and under the judicially created doctrine of obviousness-type double patenting as being unpatentable over USSN 08/760,447 have been obviated by the abandonment of USSN 08/760,447.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Patent Examiner
Technology Center 1600
March 27, 2000